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Bone Marrow Mast Cell Disease Associated With Felty's Syndrome and Liver Cirrhosis

To the Editor: Disorders with mast cell proliferation, or so-called mastocytosis are rare [1]. Mastocytosis may be localized, limited to a single organ, or affect multiple organs such as skin, gastrointestinal tract, lymph nodes, liver, spleen, bone, and bone marrow [2], and histological diagnosis is necessary for confirmation [3]. Bone marrow mastocytosis is a prominent feature of primary mast cell disorders and has also been associated with a variety of hematologic and nonhematologic conditions such as chronic lymphoproliferative disorders, acute myeloid leukemia, aplastic anemia, bone marrow fibrosis, and osteoporosis [4]. In this report, we describe a rare case of mastocytosis in the bone marrow in a patient with Felty's syndrome and liver cirrhosis.

A 61-year-old woman was referred to our hospital because of pancytopenia. She had a 10-year history of seropositive rheumatoid arthritis that had been treated with intramuscular sodium aurothiomalate weekly and nonsteroidal antiinflammatory agents. Results of a general examination were unremarkable except for bilateral swollen knee joints with pain, and a nontender spleen that was palpable five cm below the costal margin. Laboratory data were as follows: hemoglobin concentration of 8.7 g/dl; a leukocyte count of 1.9×10^9/l with a differential of 46% neutrophils, 12% eosinophils, 34% lymphocytes; and a platelet count of 120×10^9/l. Aspartate aminotransferase and alanine aminotransferase were 34 international unit (IU)/l and 21 IU/l, respectively. Alkaline phosphatase was increased to 438 IU/l (normal range, 1–340). Serum rheumatoid factor was present at 86 IU/l (normal range, 0–20), but C-reactive protein level was under 0.5 mg/dl. Serum complement C3 and C4 levels were within normal limits and total protein level was 7.6 g/dl with an albumin of 3.8 g/dl. Hepatitis C virus antibody was positive. Bone marrow aspiration from the sternum showed a normal myeloid/erythroid ratio of 1.6:1. The differential count was 1.4% myeloblasts, 4.3% promyelocytes, 14.4% myelocytes, 7.2% metamyelocytes, 10.6% neutrophils, 10.4% eosinophils, 0.5% basophils, 3.4% monocytes, 13.6% lymphocytes, and a marked increase in the number of mast cells (0.6%) (Fig. 1). Abdominal computed tomography and ultrasonography revealed marked splenomegaly. She was subsequently diagnosed as having Felty's syndrome, and an elective splenectomy was performed. A 670 g spleen measuring $17 \times 15 \times 7$ cm was removed. The histological appearance of the excised spleen revealed reactive follicular hyperplasia of the white pulp in which dilatations of the sinus were detected. These findings were compatible with a diagnosis of Felty's syndrome. A liver biopsy was also performed during surgery that revealed cirrhosis with abundant micronodular pseudolobules. However, no evidence of mast cells was detected in either the spleen or liver. After splenectomy, the patient's hematologic abnormalities showed prompt improvement: a hemoglobin concentration of 10.2 g/dl, a leukocyte cell count of 8.3×10^9/l, and a platelet count of 446×10^9/l. However, bone marrow aspiration showed only a small decrease in the number of mast cells (0.4%).

Bone marrow mast cells were evident in this case, although she did not have any symptoms corresponding to mastocytosis in previous reports (pruritus, flushing, gastrointestinal symptoms) [1]. Mastocytosis without cutaneous manifestations are rare, accounting for approximately 1.0% of all cases [1]. Mastocytosis however, tends to mimic other disorders. Regarding the mechanism of mast cell proliferation in our case, both Felty's syndrome and liver cirrhosis may affect mast cell numbers in the bone marrow. Some reports have documented both intrahepatic mast cell infiltration in chronic liver disease [5], and splenomegaly with mast cell contents [2], although no mast cells were evident in the liver or spleen tissue specimens in our case. To our knowledge, there have been no previous reports of a correlation between mastocytosis and Felty's syndrome with liver cirrhosis. It remains unknown when mast cell proliferation occurred in the bone marrow. This is nevertheless a unique case presenting withmast cell proliferation in the bone marrow, in which the possible role of Felty's syndrome, or liver cirrhosis on mastocytosis, remains to be clarified.

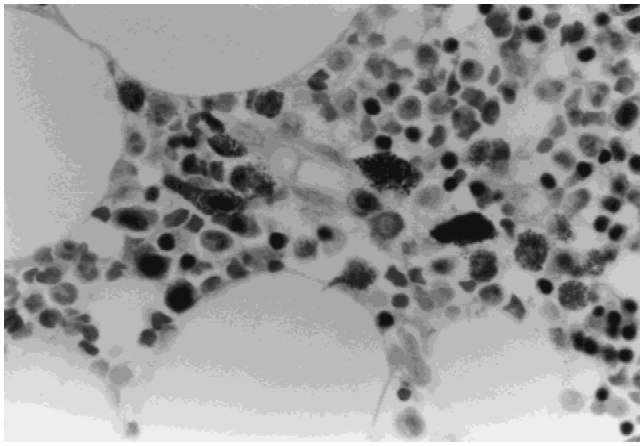

Fig. 1. Bone marrow aspiration showing an aggregation of mast cells (hematoxylin and eosin stain, ×200).

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Prothrombin Gene 20210 G-A Mutation in Turkish Patients With Thrombosis

To the Editor: Recent studies have demonstrated that common mutations in the genes encoding coagulation factor V (FV Leiden) and prothrombin

TABLE I. Patients With Prothrombin 20210 A Mutation*

Case	Age (sex)	Prothrombin 20210 A	FVL mutation	MTHFR 677 C-T	Family history	Site of thrombosis
1. RI	28 (M)	Heterozygous	Heterozygous	+/−[a]	+	Pulmonary emboli + cerebral thrombosis 6
2. AG	38 (M)	Heterozygous	Heterozygous	−/−	−	Venous thrombosis
3. MG	36 (F)	Heterozygous	Normal	+/+[b]	+	Deep venous thrombosis
4. TT	14 (M)	Heterozygous	Normal	−/−	−	Cerebral thrombosis
5. IK	15 (F)	Heterozygous	Normal	−/−	−	Venous thrombosis + CMML
6. HY	11 (F)	Heterozygous	Normal	+/−	+	Intracardiac thrombosis + cardiomyopathy + CMML

*FVL, factor V Leiden; MTHFR, methylenetetrahydrofolate reductase; M, male; F, female; CMML, chronic myelomonocyter leukemia.
[a]Heterozygous for 677 C-T mutation.
[b]Homozygous for the mutation.

(PT 20210 A) predispose individuals to increased risk of venous thrombosis [1,2].

We previously reported on a series of children with thrombosis who had factor V Leiden (FVL) mutation (50%); however, they were not examined for the 20210 A mutation [3]. The prothrombin 20210 A mutation in the present study was investigated to determine what extent this mutation influences the Turkish patients with thrombosis.

Sixty-six patients with thrombosis (15 adults and 51 children) and 87 healthy controls were screened for the prothrombin 20210 A mutation.

Blood sampling, DNA isolation, determination of the FVL, and methylenetetrahydrofolate reductase (MTHFR) 677 C-T mutations were performed as previously described [2,4]. The presence of 20210 G to A transition of the prothrombin gene was determined by *Hind*III cleavage of a 345 bp fragment amplified by polymerase chain reaction (PCR) as described previously [1].

Two heterozygote carriers of the prothrombin gene 20210 A mutation were identified in 87 control subjects (2.2%). The allelic frequency was 1.1%. In the study group of 66 patients with thrombosis, three of 15 thrombotic adults (20%) and three of 51 thrombotic children (5.8%) had 20210 A mutation. Overall frequency of the mutation in patients with thrombosis was 9%. No homozygous 20210 AA carriers were found. The frequency of the prothrombin 20210 A mutation in patients with thrombosis and in healthy controls has been found similar to previously reported studies [1,5].

The data of six patients with 20210 A mutation is shown in Table I. Three of six patients with the prothrombin mutation had either heterozygosity for FVL (33%) or homozygosity for MTHFR 677 C-T mutations (16%). The coexistence of the prothrombin gene variant with FVL and MTHFR 677 C-T mutations may cause an increased thrombotic risk in patients with thrombosis. Hillarp et al. [6] studied 99 unselected patients with deep venous thrombosis whose ages were above 62 years for prothrombin gene variant and found seven patients (7.1%) with the 20210 A mutation. They concluded that the prothrombin mutation was especially important in the pathogenesis of thrombosis in older age. In the present study, three of 51 children (5.8%) had prothrombin 20210 A mutation. This might also indicate the importance of the prothrombin gene mutation for development of thrombosis in children. Deficiencies of PC, PS, and AT III were altogether accountable for 10–15% of thrombotic patients, indicating that the prothrombin 20210 A mutation (9%) itself is an important marker for increased thrombotic risk. Therefore, we suggest that in addition to the PS, PC, AT III, and FVL mutations, the prothrombin gene mutation should also be studied in both children and adults with thrombosis.

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